EXHIBIT D

#4
11/18/92

91-318

UNITED STATES PATENT AND TRADEMARK OFFICE

J. Spear

Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No. 07/800,549

Filed: November 27, 1991

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

RESPONSE

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

October 22, 1992

Sir:

In the Office Action dated April 30, 1992, the Examiner rejected claims 1-17 of the above-identified application under 35 U.S.C. §103 as being unpatentable over Goldie et al. (U.S. 4,990,341) in view of Oshlack (U.S. 4,861,598). In making this rejection, the Examiner relied upon Goldie as teaching a controlled release oral dosage form of hydromorphone, wherein the active ingredient is in a controlled release matrix, wherein peak plasma levels are attained between 2.25 and 3.75 hours. The Examiner further stated that this reference discloses conventional matrix forming materials, coating materials, and conventional granulation processes. Finally, the Examiner stated that the Goldie reference teaches "dosage ranges which are the same as those of applicants."

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STEINBERG & RASKIN

BY: _____

The Examiner concluded that "[a]lthough Goldie does not use oxycodone, both oxycodone and hydromorphone being derivatives of natural alkaloids with many structural similarities are considered interchangeable in the matrix compositions."

The Examiner cited Oshlack as teaching matrix compositions as those of applicants' wherein the active agent is oxycodone. The Examiner concluded that it "would have been obvious to one of ordinary skill in the art to use oxycodone in the Goldie et al. invention. The motivation to do so is suggested by a desirability to provide optimum drug bioavailability by controlled release from a matrix composition."

Applicants respectfully traverse the rejection on the merits for the following reasons.

1. **Controlled Release Opioid Analgesics Have a Wide Range of Appropriate Dosages to Manage Pain**

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment

of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined.[1]

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

2. **The Oxycodone Formulations of the Present Invention Provide Surprisingly Improved Results**

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours - around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

Morphine, which is considered to be the prototypic opioid analgesic, has also been formulated into a 12 hour controlled-release formulations (i.e., MS Contin®, commercially available from The Purdue Frederick Company). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately 1/2 the dosage range as compared to seemingly similar controlled release

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[1] The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions...."

morphine formulations to control 90% of patients with significant pain.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mu-agonist analgesic to another regardless of the dosage of the former. Unless the dose response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

3. **The Present Invention Provides Important Clinical Advantages**

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain as compared to other opioid analgesics, requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

4. **The Results Obtained by the Present Invention are Not Obvious From the Prior Art**

It is respectfully submitted that one skilled in the art having knowledge of the controlled release oxycodone formulations of Goldie, et al. would not be motivated to prepare controlled release oxycodone formulations in a dosage range from about 10 mg to about 40 mg, which formulations thereby acceptably control pain over a substantially narrower, approximately four-fold range in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients utilizing controlled release hydromorphone, or controlled release opioid analgesics in general. One skilled in the art would certainly not arrive at this surprising result without the benefit of hindsight.

In view of the arguments presented, it is respectfully submitted that the Examiner's rejection on the merits has been overcome and should be removed.

An early and favorable action on the merits is earnestly solicited.

Respectfully Submitted,

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